The Emerging Role of Post-prandial Hyperglycaemic Spikes in the Pathogenesis of Diabetic Complications

Antonio Ceriello*

Department of Pathology and Medicine, Clinical and Experimental, Chair of Internal Medicine, University of Udine, Udine, Italy

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Introduction

There is general agreement that the ideal treatment of diabetic patients should restore plasma glucose levels to the 'normal range', correcting both post-prandial hyperglycaemic peaks and the less elevated by persistently high plasma glucose level between meals. In common medical practice this goal is elusive, because of practical difficulties and the risk of hypoglycaemia. Moreover, the clinical usefulness of optimizing glycaemic control has long been suggested by logic rather than supported by evidence. Eventually the large-scale prospective clinical trial of intensified vs conventional therapy, the American Diabetes Control and Complications Trial (DCCT), gave a definitive answer to the question of the efficacy of intensive treatment in preventing diabetic complications.[1] It also gave us some reference values to predict the risk of hypoglycaemia and related morbidity inevitably associated with efforts to approach normoglycaemia in diabetic patients.[2,3]

In 1993, the DCCT research teams reported that the incidence of complications was reduced by lowering the glycated haemoglobin, a reflection of mean blood glucose levels.[1] More recently, they published data on the relationship between the glycated haemoglobin value and the risk of complications, and concluded that '. . .mean HbA_{1c} is not the most complete expression of the degree of hyperglycemia. Other features of diabetic glucose control, which are not reflected by HbA_{1c}, may add to or modify the risk of complications. For example, the risk of complications may be more highly dependent on the extent of postprandial glycemic excursions. . .'[4]

Chronic hyperglycaemia is most likely to be an important pathogenetic cause of microangiopathic, and probably macroangiopathic, diabetic complications. However, since a quick and large increase in the blood glucose level, particularly in the post-prandial phase, is a typical and frequent event in the life of diabetic patients, it is surprising how little attention researchers have paid to post-prandial glycaemic spikes as possible contributors to complications. Quantifying acute variations of glucose plasma level in diabetic patients is a difficult task, so that at present insufficient data are available to define precisely the role of hyperlgycaemic spikes in the course of diabetes.

While looking forward to further data from prospective studies in man, we do have some information on the effects of an acute rise of glucose concentration from *in vitro* and animal models as well as from studies in healthy and diabetic humans. In many of these studies the glycaemic variations are comparable to those encountered in the post-prandial phase in diabetic patients. The following review highlights available evidence on the relationship between acute glycaemic variations and phenomena known or suspected to be related to diabetic complications, together with problems in diabetes care related to acute hyperglycaemia. The review is based on peer-reviewed publications found from a MedLine search based on key words hyperglycaemia and/or acute hyperglycaemia and/or post-prandial hyperglycaemia, from 1960 to January 1997.

Acute Hyperglycaemia and Microangiopathic Complications

Nephropathy

High blood glucose levels contribute to the genesis of glomerular hyperfiltration,[5] a phenomenon which is known to precede the occurrence of diabetic kidney disease.[5,6] An acute increase in blood glucose level produces an increase in glomerular filtration rate (GFR) in diabetic patients,[7] which is greater in patients with proteinuria than in patients with normoalbuminuria.[7,8]

* Correspondence to: Dr Antonio Ceriello, Department of Pathology and Medicine, Clinical and Experimental, Chair of Internal Medicine, University of Udine, P.le. S.Maria della Misericordia I-33100 Udine, Italy

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In other words, acute hyperglycaemia causes a more severe change in patients already affected by nephropathy. It is interesting to note that the acute glucose-induced increase in GFR has an extremely rapid onset and persists as long as does the hyperglycaemia.[9] There may be other effects of acute hyperglcaemia in the kidney. *In vitro* it has been demonstrated that intermittent exposure of mesangial cells to high glucose levels is a greater stimulus to hyperproduction of collagen than the chronic exposure.[10] The stimulation of mesangium to hyperproduce collagen is considered an important event in the pathogenesis of diabetic nephropathy.[11]

These observations seem to be consistent with a study of 52 patients with Type 1 diabetes, observed between 1965 and 1983, which demonstrated a relationship between the annual medians of post-prandial glucose and the time interval between the onset of diabetes and the development of nephropathy.[12]

Retinopathy

It has been shown that a condition of hyperperfusion of the retinal circulation is an important pathogenetic factor in the occurrence and progression of diabetic retinopathy,[13] and that hyperglycaemia plays a key role in increasing retinal perfusion.[14] Variations in blood flow in the retinae of diabetic patients closely parallels plasma glucose levels.[15,16] A direct effect of hyperglycaemia on retinal circulation was confirmed by studies conducted in animals, where induction of hyperglycaemia uniformly caused an increase in retinal blood flow.[17,18]

Neuropathy

Hyperglycaemia is a determining factor in the occurrence of diabetic neuropathy. Clinical studies have demonstrated that improving the control of blood glucose concentrations can stop and/or reduce manifestations typical of this pathology.[19–21] Acute hyperglycaemia in Type 1 diabetes at onset, or during rapid decompensation in chronic diabetes impairs the motor and sensory nerve conduction velocity.[22,23] The direct role of hyperglycaemia in the impairment of nerve function has been confirmed in normal subjects made acutely hyperglycaemic by clamp techniques.[24,25] In terms of symptoms, acute hyperglycaemia can lower the pain threshold in both experimental animals[26] and in patients with diabetes[27] and may have a role in the genesis of neuropathic pain. Fluctuations of blood glucose level, also in the direction of hyperglycaemia, are associated with rapid variations in mood, which may in turn influence the patient's compliance to therapy.[28]

Gastro-intestinal Tract

The advent of newer and more sophisticated diagnostic techniques have shown that abnormalities of gastric motility are common in diabetes mellitus, occurring in about 50 % of patients.[29] An increase in plasma glucose concentration delays gastric emptying,[30,31] so that apparent gastroparesis may be related to the direct effect of hyperglycaemia and not necessarily to the presence of a neuropathy.[29] Even small increases in blood glucose level impair antral motility in normal subjects.[32–34]

Such alterations induced by hyperglycaemia may have a marked impact on the already difficult task of co-ordinating therapy, either with insulin or with oral hypoglycaemic agents with the post-prandial glycaemic peak.[29] Delayed absorption of food combined with potential difficulties resulting from the altered kinetics of oral medications. There is evidence that the absorption of oral hypoglycaemic agents is delayed in the presence of gastric functional alterations,[35,36] some of which may be secondary to hyperglycaemia, as described above. This is particulary true for glipizide and glibenclamide, delayed absorption of both being directly related to the patients' blood glucose levels.[35,36] Acute hyperglycaemia has a direct influence also on the motility of other parts of the gastroenteric system, including oesophagus[37] and the gallbladder.[38,39] The reduced contractility of the gallbladder may in turn contribute to the formation of stones, the frequency of which is increased in diabetic patients.[40]

Acute Hyperglycaemia and Macroangiopathic Complications

The pathogenetic role of glucose in cardiovascular diseases and hypertension is increasingly evident, as confirmed by epidemiological studies carried out both on diabetic and non-diabetic patients.[41] There is a close association between diabetes mellitus and arterial hypertension,[42] to which hyperglycaemia may be considered a contributory cause.[43,44] A possible influence of acute hyperglycaemia on vasodilation has been suggested by many studies both *in vitro* and *in vivo*. *In vitro*, high glucose concentrations reduce acetylcholine-induced vasodilation.[45] This effect is obtained acutely by exposing samples of vessel wall to high glucose and is concentration dependent.[46] *In vivo* studies demonstrate that acute hyperglycaemia increases blood pressure, in diabetic patients as well as in normal subjects.[25–47]

There is substantial evidence that acute hyperglycaemia during myocardial infarction[48,49] and stroke[50,51] is associated with an unfavourable prognosis, in non-diabetic as well as in diabetic subjects. Although this needs clarification to determine a cause and effect relationship, a direct role of acute hyperglycaemia is supported in the case of stroke by studies in animals[52] and in diabetic as well as non-diabetic humans,[53] all showing that higher blood glucose concentrations following stroke can aggravate neuronal damage. Moreover, strict glycaemic control, obtained by multidose insulin regimen, during and after myocardial infarction may improve prognosis in diabetic patients.[54]

Acute variations of blood glucose levels are

accompanied by a series of alterations of the coagulation system, favouring thrombophilia. After the induction of hyperglycaemia both in diabetic and non-diabetic subjects, the half-life of fibrinogen is shortened,[55] while fibrinopeptide A,[56,57] the fragments of prothrombin[58] and factor VII[59] increase. Thus, data obtained in experimental acute hyperglycaemia demonstrate activation of the coagulation process. It has also been shown in diabetic patients that hyperglycaemia following normal meals causes over-production of thrombin, proportional to the blood glucose level.[60] These phenomena probably contribute to the increased thrombotic risk in diabetic subjects compared with their non-diabeic peers.[61]

Adhesion proteins regulate the interaction between endothelium and leukocytes.[62] They are involved in the process of atherogenesis because an increase in their expression on the endothelial surface causes increased adhesion of leukocytes, in particular monocytes,[63] one of the first steps in the process which leads to atheroma. Among the various pro-adhesion proteins, a special concern was aroused by ICAM-1. The soluble form of ICAM-1 accumulates in cells and may be rapidly expressed on their surface after various stimuli.[62] The circulating form of this molecule was found to be increased in subjects with vascular disease[64] and in diabetes mellitus with or without vascular disease,[65,66] and can be considered a marker of the activation of the atherogenetic process.[67] Acute hyperglycaemia in diabetic subjects has been reported to be a sufficient stimulus to increase circulating levels of ICAM-1, thus activating atherogenesis.[68]

Possible Pathogenetic Mechanisms

The mechanisms through which acute hyperglycaemia exerts its effects may be identified in labile non-enzymatic glycation and in production of free radicals. It is likely that the two mechanisms co-operate in causing the disorders of hyperglycaemia.

In labile glycation, glucose binding by a non-enzymatic reaction to the amine group of an amino acid forms a Schiff base.[69,70] This reaction proceeds as a function of both glucose concentration and time of exposure to glucose and is reversible.[69,70] If the amino acid involved in glycation is fundamental for the function of the protein, the latter will be impaired. Since the bond is reversible, the activity of the protein is restored when the blood glucose level decreases.[71] Experiments to support this mechanism are available for many biological molecules.[71] Oxidative stress is an acknowledged pathogenetic factor in diabetic complications.[72] The production of free radicals during an acute rise of blood glucose concentration may occur during labile glycation[73] or directly from glucose through a mechanism of auto-oxidation.[74] Several studies report that free radicals may be the mediators of the effects of acute hyperglycaemia. In diabetes, reductions of plasma TRAP (Total Radical-Trapping Antioxidant Parameter) levels have been reported.[75,76] During meal-induced hyperglycaemia, both in non-diabetic and diabetic subjects, there is a reduction of plasma TRAP,[77] which supports the hypothesis that plasma glucose elevations generate an oxidative stress capable of consuming the natural anti-oxidant defences of plasma. Moreover, some of the other potentially adverse effects acutely induced by hyperglycaemia, such as vasoconstriction,[25–27] activation of coagulation[58] and the increase of ICAM-1 plasma level[68] can be counteracted by antioxidants.

Conclusions

Even omitting the *in vitro* studies, which may examine non-physiological conditions, the data reported so far prove that hyperglycaemia can acutely induce alterations of normal homeostasis in animals and humans. It must be stressed that an acute increase in blood glucose level has been shown to produce alterations not only in healthy, basally euglycaemic subjects, but also in diabetic subjects whose baseline plasma glucose is in the hyperglycaemic range.

Acute increases in blood glucose level appear to be harmful events. It is now apparent that good glycaemic control from the start of treatment is essential in order to reduce the risk of late complications in the diabetic patients. However, even patients with well-controlled diabetes can go on to develop complications. This may be the result of the cumulative effects of post-prandial hyperglycaemic episodes which are difficult to control by conventional diabetic therapy. Even with good dietary practice and pharmacological control, post-prandial hyperglycaemia occurs. We are not yet able to define the relative importance of acute hyperglycaemia versus chronic hyperglycaemia in the pathogenesis of diabetic complications. Nevertheless, such information may turn out to be of the utmost clinical importance, since the post-prandial hyperglycaemic variation is an exceedingly frequent event in the life of diabetic patients with its treatment is partly different from the traditional one. There are now two drugs with particular potential for reducing post-prandial hyperglycaemic spikes: insulin lispro and acarbose. The former is a modified insulin which is rapidly absorbed from the injection site and acts faster than regular insulin,[78] whereas the latter slows intestinal glucose absorption by inhibiting alpha-glucosidase activity.[79] These two drugs, may provide new research tools to explore the impact on diabetic complications of treatments focused on post-prandial hyperglycaemia. The development of 1,5-anhydro-d-glucitol, as a useful marker of the daily excursion of blood glucose,[80,81] may facilitate such studies.

As DCCT researchers very recently underscored, there is no firm evidence to support the existence of a glycaemic threshold for the development of diabetic complications.[82] Therefore, attempting to achieve as normal as possible blood glucose levels in diabetic patients, not only in the morning or in daily averages,

but even in the post-prandial phase, may be the next imperative.

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